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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/674,752		Johannes Jacobus Voorberg	294-86	5298

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EXAMINER	
HADDAD, MAHER M	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 08/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/674,752	VOORBERG ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 July 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-59,67,68,70-73,76-80 and 82-86* is/are pending in the application.

4a) Of the above claim(s) *19,21-59,80 and 82-84* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17,18,20,67,68,70-73,76-79,85 and 86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 7/15/04, is acknowledged.

2. Claims 17-59, 67, 68, 70-73, 76-80 and 82-86 are pending.

3. Claims 19, 21-59, 80 and 82-84 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

4. Claims 17, 18, 20, 67, 68, 70-73, 76-79, 85 and 86 are under consideration in the instant application as they read on a polypeptide capable of specific binding to factor VIII and interference with the activity of factor VIII inhibitors, which polypeptide comprises the variable part of the heavy chain of a human antibody with factor VIII specificity or part thereof which at least includes the CDR3 region and a pharmaceutical composition thereof and DP-10 as the species.

5. In view of the amendment filed on 7/15/04, only the following rejections are remained.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 17, 18, 20, 67, 68, 70-73, 76-79, 85 and 86 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polypeptide capable of specific binding to factor VII and interference with the activity of factor VIII inhibitors, wherein the polypeptide comprises a heavy chain variable region of a human antibody with factor VIII specificity and a light chain variable region of a human antibody and a composition thereof, does not reasonably provide **enablement** for a polypeptide capable of specific binding to factor VII and interference with the activity of factor VIII inhibitors, wherein the polypeptide comprises a heavy chain variable "part" of a human antibody with factor VIII specificity and a light chain variable "part" of a human antibody in claim 17, wherein said polypeptide is a single chain Fv fragment comprising the heavy chain variable "part" of a human antibody with factor VIII specificity and a light chain variable "part" of a human antibody in claim 18, a pharmaceutical composition thereof in claims 20 and 81, or a method of producing said polypeptide in claims 85-86. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim for the same reasons set forth in the previous Office Action mailed 1/20/04.

Applicant's arguments, filed 7/15/04, have been fully considered, but have not been found convincing.

Applicant contends that claim 17 now expressly recites that the claimed polypeptide comprises a human antibody heavy chain variable part of a human antibody with factor VIII specificity and a human antibody light chain variable part. However, it is unclear what parts of the V_H and V_L are claimed that would lead to a polypeptide capable of specifically bind to FVIII and interference with the activity of FVIII inhibitors (FVIII antibodies).

Applicant points to Example 2 of the specification, on page 19 for support and the specific scFv fragments such as svFv-EL-14 and VHEL-14. However, the specification on page 19, example 2, discloses that the light chain variable region is derived from a human antibody not a part of the variable region. Similarity, those specific scFv comprises both the V_H and V_L regions not parts of the V_H and V_L.

Regarding the pharmaceutical compositions, applicant submits that a person having ordinary skill in the art would expect in vivo efficacy.

However, it has been established that in the absence of a correlation between the in vitro and in vivo efficacy the person having ordinary skill in the art has not basis for perceiving these efficacy. "First, although appellants' specification describes certain in vitro experiments, there is no correlation on this record between in vitro experiments and a practical utility in currently available form for humans or animals. It is not enough to rely on in vitro studies where, as here, a person having ordinary skill in the art has no basis for perceiving those studies as constituting recognized screening procedures with clear relevance to utility in humans or animals" (emphasis added). Ex parte Maas, 9 USPQ2d 1746.

8. The following new ground of rejection is necessitated by the amendment submitted 7/15/04.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 17, 18, 70-73, 76-79 and 85-86 are rejected under 35 U.S.C. 102(b) as being anticipated by Davies (Davies et al 1997, thromb. Haemostas. Supplement: 2352).

Davies et al teach eight human FVIII specific scFvs were selected by panning on immobilized rFVIII. Further, Davies et al teach obtaining the immunoglobulin V(ariable) domain structure of immune FVIII antibodies obtained by V gene phage display technology from 3 Haemophilia A patients with peak inhibitor levels about 60Bu/ml. Davies et al teaches that 3 patients have antibodies against the A2 domain and 2 patients have antibodies to the light chain. Davies et al teach the method of producing a recombinant scFvs specific for Factor VIII by obtaining the primary structure of the variable domains of factor VIII antibodies obtained from inhibitor

patient B cells RNA by V gene phage display technology. The VH gene cDNA was obtained by reverse transcription of lymphocytic RNA from the 3 patients with an IgG specific primer and amplified by the PCR with appropriate VH and joining gene primers. The amplified VH gene repertoire was cloned for display as single chain V domain fragments (scFv) on the surface of the phagemid vector PhEN-2-VL. Each library contained 10^7 individual clones (see the abstract in particular).

While the prior art teachings may be silent as to the "interference with the activity of factor VIII inhibitors" in claim 17, "wherein the polypeptide reduces the activity of factor VIII inhibitors of haemophilia A patients" in claim 76, and wherein " the factor VIII inhibitors of Haemophilia A patients are antibodies specific for factor VIII" in claim 77 per se; the referenced svFv polypeptides are the same as the claimed polypeptide that is capable of specifically bind to FVIII. Therefore limitations are considered inherent properties of the referenced scFv polypeptides.

The reference teachings anticipate the claimed invention.

Applicant's arguments, filed 7/15/04, have been fully considered, but have not been found convincing.

Applicant traverses the rejection based on the ground that no disclosure or suggestion that the scFv fragments disclosed in Davies et al are capable of interfering with the activity of factor VIII inhibitors. However, given that the referenced human scFv polypeptides specifically bind FVIII and the source of Davies' human scFv antibodies derived from the same patient B cells as the claimed antibody polypeptides. Therefore, "interference with the activity of factor VII inhibitors" is considered inherent properties of the referenced human scFv polypeptides.

Regarding method of producing the polypeptide, Applicant argues that nowhere in Davies et al is there any disclosure or suggestion of a polypeptide that is capable of specific binding to factor VIII and interference with the activity of factor VIII inhibitors, and that comprises a heavy chain variable part of a human antibody with factor VIII specificity and a light chain part of a human antibody.

Contrary to applicant arguments Davies et al teach the claimed polypeptide capable of specific binding to factor VIII comprising V_H and V_L regions, wherein the referenced scFv would inherently interfere with the activity of factor VIII inhibitors. Further, Davies et al teach the method of producing a recombinant scFvs specific for Factor VIII by obtaining the primary structure of the variable domains of factor VIII antibodies obtained from inhibitor patient B cells RNA by V gene phage display technology. The VH gene cDNA was obtained by reverse transcription of lymphocytic RNA from the 3 patients with an IgG specific primer and amplified by the PCR with appropriate VH and joining gene primers. The amplified VH gene repertoire was cloned for display as single chain V domain fragments (scFv) on the surface of the

phagemid vector PhEN-2-VL. Each library contained 10^7 individual clones (see the abstract in particular).

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

11. Claim 20 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Davies et al in view of U.S Patent No. 4,731,245 for the same reasons set forth in the previous Office Action mailed 1/20/04.

Applicant's arguments, filed 7/15/04, have been fully considered, but have not been found convincing.

Applicants state that they provided arguments to refute the rejection of claims 17 and 18 over Davies et al. Applicant concluded that claim 20 is patentable over Davies et al for the same reasons that claims 17 and 18 are patentable. Further, Applicants submit that the combination of Davies et al and the `245 patent does not result in the claimed invention.

However, the Examiner's position is the same as indicated under the 102(b) rejection. Further, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to formulate the antibody fragments taught by Davies et al in a composition with a pharmaceutically acceptable carrier as taught by the `245 patent to enable the administration of the antibody at a daily dose as taught by the `245 patent

12. No claim is allowed.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maher Haddad, Ph.D.
Patent Examiner
August 20, 2004

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